REMARKS/ARGUMENTS

Applicants thank Examiner for the courtesies extended during the interview of January 14, 2004. The above claim amendments were presented. Applicants' attorney discussed how the amendments to claims 1 and 3 addressed the grounds of rejection set forth in items 6 through 8 of the Detailed Action. The arguments presented at the interview are included in the Remarks/Arguments section below. Smedts et al. was also briefly discussed. No exhibit was shown at the interview. No demonstration was presented at the interview. Agreement was reached as to allowability of all claims remaining in the application upon entry of the claim amendments.

Claim Amendments

Claims 1 and 3 have been amended to specify that the method of the present invention screens for a deviation from normality indicative of a premalignant or neoplastic disease state. There is basis for this amendment at page 1, lines 3 to 8, page 3, lines 9 to 27, page 4, lines 4 to 14 and page 25, lines 17 to 21 of the specification as filed.

Claims 1 and 3 have been amended to recite that the method refers specifically to a deviation from normality indicative of a premalignant or neoplastic disease state in the squamous cells of a cervical smear sample, and there is basis for this amendment at page 14, lines 7 to 10 and Table 4, page 55 of the specification as filed. Four of the five monoclonal antibodies (MAb) deposited are specific for squamous cells (see the table at page 17 of the specification as filed). The fifth MAb deposited (2C7) is specific for columnar cells, and is used in the method of the present invention to indicate the presence of columnar

cells in a smear sample, demonstrating that the smear is adequate (see page 38, lines 19 to 24 of the specification as filed) allowing a greater degree of confidence in the assay results. Approximately 95% of cervical tumors arise from the squamous epithelium (see page 14, lines 7 to 10 of the specification as filed). It would therefore be immediately apparent to one of ordinary skill in the art that the disease state screened in the method of the present invention is present in the squamous cells of a cervical smear sample.

Claims 1 and 3 have been amended to refer to

> "the percentage of the monoclonal antibody or antibodies specific for squamous cells binding to abnormal squamous cells is increased or decreased with respect to the binding of the said monoclonal antibody or antibodies to normal squamous cells in the cervical smear sample".

There is basis at page 34, lines 8 to 9 and 13 to 17, and at page 47, lines 15 to 19 of the specification as filed for the amendment specifying that the binding of the monoclonal antibody or antibodies may increase or decrease. The remaining amendments have been made to improve the clarity of these Claims. There is basis for these amendments at page 6, lines 21 to 24 and page 25, line 26 to page 26, line 5 of the specification as filed.

Claim 11 has been deleted.

35 U.S.C. 112, second paragraph

Claims 1 to 4 and 10 to 12 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite.

Claim 1 was considered indefinite for failing to recite whether the binding of the monoclonal antibody specific to columnar cells increases or decreases in premalignant cells compared to normal cells.

The squamo-columanar junction is the region where the majority of malignancies arise (see page 13, lines 17 to 21 of the specification as filed), and is thus the area of most significance when screening for a deviation from normality indicative of a premalignant or neoplastic disease state. Indeed, page 14, lines 7 to 10 specifically state that 95% of cervical tumors arise from the squamous epithelium. The presence of columnar cells in a smear sample indicates that cells from the squamo-columnar junction have been sampled, and this indicates the integrity of the smear sample (see page 13, lines 19 to 23 of the specification as filed), which teaches that "For diagnostic validity, a cervical smear sample .... must contain columnar as well as squamous epithelial cells".

The present invention is concerned with a method of screening for a deviation from normality indicative of a premalignant or neoplastic disease state in the squamous cells of a cervical smear sample and the Claims have been amended accordingly. The presence of the MAb specific for columnar cells demonstrates the presence of columnar cells, indicating that the cervical smear sample has been taken correctly (see page 38, lines 19 to 23 of the specification as filed). The percentage binding of the MAb specific to columnar cells would not change due to a deviation from normality in the squamous cells, since this MAb does not bind to the squamous cells and would not therefore detect any changes in the cells. The MAb specific for columnar

cells is however important to verify the diagnostic validity of the smear sample.

Claims 2 and 3 were rejected as indefinite through the use of the term "wherein the percentage binding". Applicant notes that Claim 2 as currently on file does not contain this term and it is believed that the Examiner intended to refer to Claims 1 and 3. The percentage of the monoclonal antibody specific for squamous cells binding to premalignant or neoplastic squamous cells increases or decreases compared to the binding of this same monoclonal antibody to normal squamous cells in the cervical smear sample. Claims 1 and 3 have been amended to clarify this, and the current wording is believed to be clear.

35 U.S.C., 112, first paragraph

Claims 1 to 4 and 10 to 12 were rejected under 35 U.S.C., 112, first paragraph, as containing subject matter which was not described in the specification as filed in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention.

The Examiner stated that MAb 2C7 does not fulfil the limitation of decreased percentage binding in neoplastic disease. MAb 2C7 is specific for columnar cells (see page 38, lines 1 to 4 of the specification as filed) and is included in the claimed screening method to ensure diagnostic validity of the cervical smear sample. As noted above, the binding of the MAb specific to columnar cells (such as MAb 2C7) would indeed not change due to a deviation from normality in squamous cells. The Claims as amended do not recite that the binding of the MAb specific for columnar cells would increase or decrease upon contact with

premalignant or neoplastic squamous cells. Such abnormality is detected through the increased/decreased binding to the squamous cells of the MAb specific for squamous cells.

The Examiner notes that MAb 6B5 does not exhibit decreased reactivity to premalignant or neoplastic cervical cells. The crux of the invention is to identify cervical smear samples which show a pattern of binding which deviates from normality (see page 3, lines 9 to 14 and page 48, lines 6 to 13 of the specification as filed). The Claims have been amended to recite that the MAb specific for squamous cells exhibits an increase or decrease in binding to premalignant or neoplastic cervical cells, and thus MAb 6B5 is included in the Claims as amended.

Thus, contrary to the Examiner's assertion, the combination of MAb 6B5 and 2C7 now falls into the scope of the Claims as amended.

The Examiner asserts that the combination of MAb 9G5 and MAb HG3 does not support the Claim amendment filed Feb. 10, 2003. The specification as filed teaches that MAb 9G5 and MAb HG3 may be used in tandem to detect all squamous cell populations at all stages of the cell or oestrus cycles. The specification as filed teaches that it may be prudent to assess the binding of more than one MAb specific for squamous cells to the squamous cells of a cervical smear sample (see page 42, line 16 to page 43, line 12 of the specification as filed). The present Application teaches that MAb 9G5 and HG3 may be combined to act as MAbs specific for squamous cells referred to in the Claims as amended. There is, however, no suggestion that MAb 9G5 and HG3 make up the entire panel of MAbs used in the claimed method of screening. The specification as filed teaches the benefits

of including a monoclonal antibody specific to columnar cells (see page 38, lines 19 to 23 of the specification as filed), and that it is preferable to include a MAb specific for columnar cells in the panel, to demonstrate that cells from the squamo-columnar junction have been tested (see page 13, lines 17 to 23 of the specification as filed). The specification as filed teaches that MAb 9G5 and HG3 may be used in tandem to act as the MAb specific for squamous cells (see page 42, lines 16 to 28 of the specification as filed), and that a MAb specific for columnar cells would also be included in the panel of MAbs to ensure diagnostic validity (see page 13, lines 17 to 23 and page 38, lines 19 to 24 of the specification as filed).

The Examiner considers that the term "neoplastic" encompasses both benign and malignant tumors and that the specification as filed does not disclose that the properties reported for the deposited antibodies are consistent with a decrease in binding in malignant neoplasms. The Claims have been amended to relate to a method of screening for a deviation from normality indicative of a premalignant or neoplastic state. The pattern of binding of the MAbs to abnormal squamous cells deviates from the binding pattern to normal squamous cells (see page 47, lines 12 to 25 of the specification as filed). Applicant submits that the properties of the MAbs disclosed are consistent with the Claims as amended. For example, as recognized by Examiner (Detailed Action, page 5, line s 17-19), MAb HG3 is reactive to squamous cell carcinomas. Manifestly, a carcinoma is a malignancy. Thus, the specification exemplifies an MAb which binds cells of a malignant neoplasm.

Claim 3 was rejected for new matter for incorporating the limitation of "wherein the percentage binding of the two or

more monoclonal antibodies to premalignant or neoplastic cells is decreased with respect to normal cells". Claim 3 has been amended to specify that the binding of the MAb(s) specific for squamous cells to abnormal squamous cells is increased or decreased with respect to the binding of the same MAb(s) to normal squamous cells. Applicant submits that the objection to Claim 3 for new matter is thus overcome.

The Examiner asserts that the disclosure in the specification as filed that MAb 2C7 and 6B5 may be used in combination, and MAb 9G5 and HG3 may be used in combination, does not provide sufficient support for an amendment encompassing a genus of antibodies beyond those of the disclosed antibodies. The specification teaches that abnormality indicative of the onset of premalignant or neoplastic disease conditions of squamous cells in a cervical smear may be indicated by an increase or decrease of binding of a particular detectable cell marker to squamous cells (see page 47, lines 12 to 25). Five MAbs were deposited in connection with the present invention merely to exemplify the method of the present invention (see page 4, lines 15 to 17). Of the five MAbs disclosed to exemplify the method of the present invention, four are specific for squamous cells, one is specific for columnar cells (see table, page 17). The specification as filed teaches that it is preferable to include a MAb specific for columnar cells to demonstrate that the cervical smear has been taken correctly (see page 13, lines 19 to 23 and page 38, lines 16 to 24 of the specification as filed). The specification as filed also teaches the importance of assessing squamous epithelium as approximately 95% of cervical tumors arise from the squamous epithelium (see page 14, lines 7 to 10 of the specification as filed).

The specification as filed discloses several examples of specific antibodies, allowing discrete stages in the differentiation of squamous epithelial cells to be distinguished, and allowing the columnar cells to be distinguished from the squamous epithelial cells (see page 17, lines 15 to 20 of the specification as filed). The specification as filed teaches that four of the specific antibodies disclosed have overlapping specificities for squamous cells (see page 47, lines 3 to 7 of the specification as filed). The fifth antibody disclosed, reacts specifically with columnar cells and the specification as filed teaches that such a MAb should be present to ensure diagnostic validity (see page 13, lines 17 to 23 and page 38, line 25 to page 39 line 3).

One of ordinary skill in the art would consider that other specific binding molecules may be employed in the method of the present invention if they exhibit the properties specified in the Application, and the Application as filed specifically teaches this (see page 4, lines 21 to 28 of the specification as filed). One skilled in the art could also utilize the antibody product of the deposited hybridomas to augment the teachings of the specification, as an aid in selecting additional hybridomas producing antibody having the desired characteristics. The production of MAbs is well established in the art (see page 8, line 4 to page 9, line 3 of the specification as filed) and one of ordinary skill in the art would be able to produce other suitable MAbs without undue experimental burden given that the teaching in the specification of the present invention is not limited to the specific MAbs deposited.

Claim 11 was rejected as lacking written description. This Claim has been canceled.

35 U.S.C. 102(b)

Claims 1 and 2 were rejected under 35 U.S.C. 102(b) as being unpatentable over Smedts et al.

Smedts et al. discloses the expression of five keratins in different types of cervical tissue. Only the MAb specific for keratin 16 bound columnar cells, and Smedts et al. teach that in general columnar cells were not detected (see page 406, paragraph 1 of Smedts et al.). Keratin 16 was also detected in the basal cell compartment of CIN I samples (see page 407, column 1, paragraph 1), the basal cell compartment of CIN II samples (see page 407, column 1, paragraph 2) and the epithelium of CIN III samples (see page 407, column 2, paragraph 1). Smedts et al. teach that keratin 16 is present in reserve cells and in immature and mature squamous metaplasia (see page 409, column 2, second paragraph to page 410, column 1, first paragraph).

The monoclonal antibody specific for columnar cells in the present invention demonstrates whether columnar cells are present in the smear sample, indicating whether the smear sample properly samples cells from the squamo-columnar junction. This ensures the diagnostic validity of the smear sample (see page 13, lines 16 to 23 and page 38, lines 16 to 24 of the specification as filed).

Keratin 16 is present in columnar cells and the MAb specific for keratin 16 is the only MAb disclosed by Smedts et al. to bind to columnar cells. However, this MAb also binds to many other types of cells, including reserve cells, immature and mature squamous metaplasia and basal cells of CIN I, CIN II and CIN III samples. The presence of binding of the MAb specific to keratin 16 may indicate the presence of columnar

cells, reserve cells, immature and mature squamous metaplasia or basal cells of CIN I, CIN II or CIN III. As such testing for the binding of the MAb specific for keratin 16 provides a completely unreliable method of determining the presence of columnar cells, as the binding may result from the presence of any of the other types of cells this MAb binds to. This MAb cannot therefore be used as a reliable indication that the smear sample has sampled the squamo-columnar junction. Applicant submits that the method of the present invention is, thus, inventive over Smedts et al.

It is therefore believed that the Examiner's rejections have been overcome by the amendment of the Claims and issuance of the Patent is therefore solicited.

Respectfully submitted,

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